

# Urinary Antispasmodics: Anti-muscarinics

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2013

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## Introduction

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) describes overactive bladder (OAB) as having to void or empty the bladder more than 8 times in a day or more than 2-3 times/night (nocturia). This may be associated with the loss of large or small amounts of urine (urge incontinence). Some, but not all patients with OAB experience urinary incontinence. OAB usually results from an involuntary increase in bladder pressure due to bladder smooth muscle (detrusor) over-activity.<sup>1</sup>

Urinary tract infections (UTI), other conditions (e.g. diabetes insipidus), or factors (e.g. fluid intake, excessive nighttime urine production) are unrelated to OAB and should be excluded as these may be responsible for similar symptoms. In summary, there are 4 symptom characteristics to OAB; urgency, frequency, nocturia and urgency incontinence (in the absence of UTI, other obvious pathology, or factors).<sup>2</sup>

The major subtypes of urinary incontinence differentiated by etiology are:

- 1) Bladder overactivity (Urge incontinence)
- 2) Urethral overactivity/bladder underactivity (overflow incontinence)
- 3) Urethral underactivity (stress incontinence)

Some patients may experience mixed incontinence.

OAB affects men and women; 33 million men and women in the United States (17% of American adults); and it is more common in women (9-43% vs 7-27%)<sup>2</sup> and in older people.<sup>3,4</sup> Urgency, frequency and incontinence has a noticeable negative impact on quality of life with psychological (anxiety and depression) and social consequences (restricted activities).<sup>1</sup> Most patients have symptoms for years and it is common for patients to only seek treatment after an extended period of symptoms.<sup>2</sup>

Management of OAB includes behavioral and non-pharmacological treatment (e.g. bladder training, pelvic floor exercises, and electrical stimulation), or pharmacological treatment.<sup>4</sup> Anticholinergic drugs are the most efficacious agents for the pharmacological treatment of OAB. Anticholinergic drugs can reduce the overactivity of the bladder muscle and the feeling of urgency by inhibiting the muscarinic receptors in the bladder, which causes smooth muscle relaxation.<sup>5</sup> Oxybutynin has been used for more than 4 decades and it remains the most widely prescribed medication for OAB in the world.<sup>6</sup>

Anticholinergics are commonly used in primary and secondary care settings for the treatment of OAB and this has considerable resource implications.<sup>1</sup> Urinary Antispasmodics include some proprietary drugs and the number of anticholinergic drugs on the market is increasing.<sup>1</sup> Gelnig (aka Anturol), an oxybutynin gel became available in April 2012.<sup>7,8</sup> On 25 January 2013, the FDA approved Oxytrol for Women, the first over-the-counter treatment for overactive bladder in women ages 18 years and older and the first anticholinergic to be made available over the counter.<sup>9</sup> Also, TEVA has a vaginal ring oxybutynin in clinical development.<sup>10</sup> On June 28, 2012 the FDA announced the approval of a new treatment option; Myrbetriq (mirabegron) extended-release tablets for the treatment OAB. It is available in 25mg and 50mg dosage strengths and became available in the fourth quarter of 2012. Mirabegron is a potent and selective beta-3 adrenoceptor agonist which activates beta-3 adrenoceptors on the detrusor muscle of the bladder to facilitate filling of the bladder and storage of urine.<sup>11</sup> “At usual doses, mirabegron is believed to display selectivity for the beta-3 adrenergic receptor subtype compared to its affinity for the beta-1 and -2 adrenoceptor subtypes.”<sup>12</sup> This new class will not be discussed in this review, but in a separate review.

This review will focus on the anticholinergic treatment options for OAB. The American Urological Association (AUA) issued new guidelines in May 2012 for the treatment of OAB and it will be discussed in this review.

This review will not include the other treatment options such as behavioral approaches, neuromodulation therapies, onabotulinumtoxinA, low-dose vaginal estrogen (used to replace declining estrogen in vaginal and

urethral tissues of menopausal women with atrophic vaginitis incontinence symptoms)<sup>2</sup>, tricyclic antidepressants, and beta3 adrenoceptor agonists; or off-label uses of the OAB indicated anticholinergic drugs (such as gastrointestinal disorders).

## Management of overactive bladder (OAB) - Anticholinergics

Currently, there are six different anticholinergic medications approved by the US Food and Drug Administration (FDA) for the treatment of OAB:

- Darifenacin<sup>13</sup>
- Fesoterodine<sup>14</sup>
- Oxybutynin<sup>5</sup>
- Solifenacin<sup>15</sup>
- Tolterodine<sup>16</sup>
- Trospium<sup>17</sup>

These medications include many formulations; immediate and extended-release tablets, a transdermal patch system, a recently approved oxybutynin gel, and a vaginal ring in clinical development.

Flavoxate is indicated for the symptomatic relief of dysuria, urgency, nocturia, suprapubic pain, frequency and incontinence associated with cystitis, prostatitis, urethritis, urethrocystitis, or urethrotigonitis. It has not been shown to be more effective in the treatment of these conditions than antimuscarinic agents and it is not indicated as definitive treatment, but is compatible with drugs used for treatment of urinary tract infections.<sup>18,19</sup> Its mechanism of action is not clear; it may have local anesthetic activity and direct relaxing effects on smooth muscle as well as some activity as a muscarinic antagonist.<sup>20</sup>

### Recent FDA approvals

Gelniq (aka Anturol), an oxybutynin gel became available in April 2012.<sup>7,8</sup>

On January 25, 2013 the FDA announced that they have approved Oxytrol for Women over-the-counter (OTC) treatment for OAB in women ages 18 years and older; the safety and effectiveness for OTC use were established in nine studies (more than 5,000 subjects participating). Merck anticipates that it will be available to customers in fall 2013.<sup>21</sup> Oxytrol will be available for men with OAB by prescription only.<sup>9</sup>

## How supplied and maximum usual dosage

**Table 1. Usual and Maximum Doses of Anticholinergic OAB Medications**<sup>7,17-19,22-33</sup>

Drug	Generic	Dosage Form(s)	Usual Dose from Product Labeling	Maximal Recommended Dose per Product Labeling
<b>Anticholinergics</b>				
Darifenacin – Extended release (Enblex)	No	Tablets: 7.5 mg and 15 mg	Starting dose: 7.5 mg once daily. The dose may be increased to 15 mg once daily based on patient response. 7.5 mg in patients with moderate hepatic impairment or those taking potent CYP3A4 inhibitors.	Adults: 15 mg once daily.
Fesoterodine – Extended release (Toviaz)	No	Tablets: 4 mg and 8 mg	Starting dose: 4 mg once daily. The dose may be increased to 8 mg once daily based on individual response and tolerability. 4 mg in patients with severe renal impairment (Creatinine clearance (CLcr) <30 mL/min or those taking potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, and clarithromycin.)	Adults: 8 mg once daily.
Flavoxate (Urispas)	Marketing status: brand discontinued			
	Yes	Tablets: 100 mg	≥12 years of age: Urinary spasms: Oral: 100-200 mg 3-4 times daily; reduce the dose when symptoms improve.	≥12 years: 800 mg
Oxybutynin – Controlled-release (Ditropan XL)	Yes	Tablets: 5 mg, 10 mg, and 15 mg	Adults: Initiate therapy at 5 mg once daily. Adjust dose in 5 mg increments at weekly intervals.  Pediatric patients ≥6 years: Initiate therapy at 5 mg once daily. Adjust dose in 5 mg increments at weekly intervals.	Adults: 30 mg per day  Pediatric patients ≥6 years: 20 mg per day
Oxybutynin – Transdermal system (Oxytrol)	No	Patch: 3.9 mg/day	Apply one patch twice weekly (every 3-4 days) to dry, intact skin on the abdomen, hip, or buttocks. Avoid reapplication to the same site within 7 days.	Not stated. One patch twice weekly (usual dose).
Oxybutynin – Transdermal (Gelnique / aka	No	Metered gel 3% 10%(100 mg/packet)	3 pumps of GELNIQUE 3% (84 mg) OR Apply contents of one sachet of GELNIQUE once daily to clean and dry, intact skin on the	3 pumps or one sachet once daily

Anturol)			abdomen, or upper arms/shoulders, or thighs.	
Solifenacin (VESicare)	No	Tablets: 5 mg and 10 mg	Initiate therapy at 5 mg once daily. The dose may be increased to 10 mg once daily based on patient response and tolerability. 5 mg tablet once daily in patients with severe renal impairment (CLcr <30 ml/min), moderate hepatic impairment or concomitant use of potent CYP3A4 inhibitors.	Adults: 10 mg once daily
Tolterodine – Immediate-release (Detrol)	Yes	Tablets: 1 mg and 2 mg	Initiate therapy at 2 mg twice daily. The dose may be decreased to 1 mg twice daily based on response and tolerability. Patients with significantly reduced hepatic or renal dysfunction or patients taking potent CYP3A4 inhibitors should take 1 mg twice daily.	Adults: 4 mg per day
Tolterodine – Controlled-release (Detrol LA)	No	Capsules: 2 mg and 4 mg	Initiate therapy at 4 mg once daily. The dose may be decreased to 2 mg once daily based on response and tolerability. 2 mg capsules once daily in patients with mild to moderate hepatic impairment, severe renal impairment [CLcr 10-30 mL/min] or drugs that are potent CYP3A4 inhibitors.	Adults: 4 mg per day
Tropium chloride (Sanctura)	Yes	Tablets: 20 mg	Initiate therapy at 20 mg twice daily. The dose may be decreased to once daily in patients ≥ 75 years of age based on tolerability. Severe renal impairment (CLcr < 30 mL/min): 20 mg once daily at bed time.	Adults: 20 mg twice daily
Tropium chloride (Sanctura XR)	Yes	Capsules: 60 mg	60 mg orally once daily in the morning.	Adult: 60 mg

## Safety and adverse effects

Anticholinergics used in OAB are not specific to the muscarinic receptors in the bladder and can cause side effects by acting in other parts of the body too (e.g. gut, salivary glands, tear ducts, brain and heart), causing for example dry mouth or eyes, constipation, or nausea. These anticholinergic effects are often described colloquially as:

“Blind as a bat (mydriasis/blurred vision), mad as a hatter (psychosis, confusion, decreased cognitive function), red as a beet (flushing), hot as a hare (hyperthermia), dry as a bone (dry mouth, eyes and skin), the bowel and bladder lose their tone (constipation, urinary retention), and the heart runs alone (tachycardia, hypertension).”<sup>34</sup>

Because of these effects, anticholinergic medications are contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma, and in patients who are at risk for these conditions.<sup>22,24,27,28,30,32</sup>

The concomitant use of anticholinergics with other anticholinergic agents may increase the frequency and/or severity of dry mouth, constipation, blurred vision and other anticholinergic effects.<sup>22</sup>

Safety and efficacy has not been established for use in children for any of these drugs apart from oxybutynin ER (children  $\geq 6$  years).<sup>22,24,27,28,30,32</sup> The BEERS Criteria include anticholinergics as potentially inappropriate in elderly patients ( $> 65$  years) and the quality and strength of the recommendation varies based on comorbidities. Caution should be used due to the anticholinergic effects and it is recommended to start treatment at lower doses.<sup>35</sup>

Please refer to the product labeling for complete prescribing information.

Most pharmacologic studies reported rates of dry mouth and constipation, but did not report on cardiac or cognitive adverse events which is a limitation in the currently available published literature.<sup>2</sup>

## Clinical Efficacy

There has been some uncertainty about anticholinergic drugs used in OAB in terms of efficacy, at what dose, route of administration, and its role in different patient groups (the elderly, men and women).<sup>1</sup>

### American Urological Association (AUA) Guideline<sup>2</sup>

This guideline was written by the Overactive Bladder Guidelines Panel of the American Urological Association Education and Research, Inc. and included urologists and other clinicians with specific expertise on this disorder. It was funded by the AUA and the Society for Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction and committee members received no remuneration for their work.

“This guideline’s purpose is to provide direction to clinicians and patients regarding how to recognize non-neurogenic OAB, conduct a valid diagnostic process and approach treatment with the goals of maximizing symptom control and patient quality of life while minimizing adverse events and patient burden.”<sup>2</sup> It was not intended to be interpreted rigidly and an individualized approach for a particular patient is suggested as the most effective approach.

## Reference documents for review

Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults: AUA/SUFU Guideline (2012)

- [http://www.auanet.org/content/media/OAB\\_guideline.pdf](http://www.auanet.org/content/media/OAB_guideline.pdf)

## Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults: AUA/SUFU Guideline Algorithm (2012)

- [http://www.auanet.org/content/media/OAB\\_algorithm.pdf](http://www.auanet.org/content/media/OAB_algorithm.pdf)

### Sources of evidence for guideline (for majority of treatment portion):

- Primary source: Systematic review and data extraction conducted as part of the Agency for Healthcare Research and Quality (AHRQ) Evidence Report/Technology Assessment Number 187 titled Treatment of Overactive Bladder in Women (2009)<sup>36</sup> (literature search: Jan 1966 – Oct 2011)
- Additional literature searches by AUA (for treatments not covered and articles published between Oct 2008 and Dec 2011)
- All these studies (including those excluded in the primary source) were added to the database and the AUA performed its own qualitative and quantitative analyses of the extracted data including meta-analyses as appropriate

### Summary of recommendations for treatment portion of guideline that involves urinary antimuscarinics:

151 articles regarding treatment met the inclusion criteria.

The first part of the guideline (statement 1-3) covers the diagnostic process (through careful history, physical exam, urinalysis) to exclude other disorders, fluid intake habits (quantity of fluids, caffeine), and medication use (e.g. diuretics). Clinicians should consider referring complicated patients (defined in guideline statement 1) to a specialist for further evaluation and treatment.

The guideline statements in section 6 are regarding treatment and serves as a “framework to assist the clinician in counseling patients and in developing an individualized treatment plan that optimizes quality of life.”<sup>2</sup> The panel considered benefits versus risks/burdens (invasiveness of treatment and duration, severity and reversibility of potential side-effects) when they prepared the hierarchy of treatment (first to fifth-line groups) and not the number of available studies or evidence strength.

For some patients and clinicians, ‘no treatment’ is an acceptable choice. Various individual factors need to be considered when selecting treatment options for a particular patient. The clinical effectiveness of treatment is dependent on efficacy (desired change in symptoms), tolerability (adverse effects) and compliance.<sup>2,37</sup> Patients may be unwilling or unable to comply with behavioral therapy regimens and instructions or drug therapy for various reasons.

“OAB is a chronic syndrome without an ideal treatment and no treatment will cure the condition in most patients”<sup>2</sup>

#### First-Line Treatments

Behavioral therapy (e.g. bladder training, bladder control strategies, pelvic floor muscle training, fluid management) should be first-line treatment in all patients with OAB. (Grade B)

Anti-muscarinics may be combined with behavioral therapy, but the evidence strength is low (Grade C) due to few trials, small sample sizes and limited follow-up durations.

#### Second-Line Treatments

- Oral antimuscarinics (Grade B)

Currently, there is no convincing evidence for superior efficacy of any of the medications in the published literature.<sup>2,38-41</sup>



- ER preferred over IR because of low rates of dry mouth (Grade B - moderate evidence)  
Decreased adverse events and once-daily dosing may increase compliance. The panel however recognized factors such as patient's prior experience and insurer constraints as factors that need to be considered when decisions are made as to prescribe IR or ER formulations.
- Transdermal oxybutynin patch or gel may be offered to patients who are at risk for or who have experienced dry mouth with oral agents, but the evidence strength is low (Grade C).  
Only a few studies evaluated the transdermal products (patch vs placebo: 4 studies; patch vs oral: 1 study; gel vs placebo: 1 study). Dry mouth rates appear to be lower than for oral oxybutynin IR and ER. More information can be found in guideline section 10.

#### *Clinical principles:*

- Dose modification or a different anti-muscarinic may be tried when symptom control is inadequate and/or adverse effects are unacceptable.

Fesoterodine<sup>42</sup>, solifenacin<sup>43,44</sup>, or darifenacin<sup>45</sup> may provide better symptom control and/or fewer unacceptable side-effects for patients who had unacceptable symptom control and/or side-effects with tolterodine or oxybutynin.

Concomitant anti-muscarinics or combinations with other classes such as tricyclics to manage non-neurogenic OAB is not covered in the published literature.<sup>2</sup>

- Patients with narrow-angle glaucoma should not receive anti-muscarinics (unless approved by the treating ophthalmologist).

Antimuscarinics in patients with impaired gastric emptying or a history of urinary retention: use extreme caution.

Concomitant antimuscarinics and potassium chloride solid dose: contraindicated as the anticholinergic could potentially cause an arrest or delay of potassium chloride tablet passage through the gastrointestinal tract, thereby increasing the risk of gastrointestinal lesions; and it may increase the potassium absorption of these agents.<sup>2,46-48</sup>

- Constipation and Dry mouth should be managed before discontinuing effective treatment (Bowel management e.g. fiber supplements, regular exercise; fluid management; preparing for dry mouth with oral lubricants, avoiding alcohol mouthwashes, sucking on sugar-free candies; dose modification; alternative antimuscarinics).

#### *Expert opinion:*

- Additive toxicity: use caution in patients who are using other medications with anticholinergic properties (e.g. antihistamines, tricyclic antidepressants, benztropine, biperiden/Akineton, ipratropium)
- Use caution in frail OAB patients (patients with mobility deficits, weight loss and weakness without medical cause, cognitive deficits). The lowest possible dose should be used as antimuscarinics may have a lower therapeutic index in these patients and patients may experience more adverse effects (not just dry mouth and constipation, but also temperature elevation for example). Other factors to consider in frail patients include the condition of the skin (for transdermal), polypharmacy, and cognitive deficits (particularly in the elderly). These drugs should be used with extreme caution or they may not be appropriate depending on the level of cognitive impairment. Some limited literature (only 2-week administration) suggests that newer agents (e.g. Darifenacin) may cause less cognitive effects in the elderly compared to older agents.<sup>49,50</sup>

Expert opinions in this guideline include follow-up with the patient to assess compliance, efficacy, side effects and possible alternative treatments.

Patients who have failed trials with behavioral and antimuscarinic therapy should be referred to a specialist if they desire additional treatment as the remaining treatment options pose greater risks to patients. These are covered as third-line treatments in the guidelines and include procedures such as neuromodulation therapies and peripheral nerve stimulation (FDA-approved), intradetrusor injection of onabotulinumtoxinA, indwelling catheters, and augmentation cystoplasty or urinary diversion.

## Cochrane Review(s)

A recent Cochrane review compared the different anticholinergic agents used in OAB.<sup>1</sup>

Table 2

Author & publication date	Title	Objectives	Studies included	Comparisons made
Madhuvrata P, et al. 2012 <sup>1</sup>	Which anticholinergic drug for overactive bladder symptoms in adults	To compare the effects of different anticholinergic drugs for overactive bladder symptoms.	86 trials: 70 parallel + 16 cross-over; 31,249 adults. Most double-blind; variable in other aspects of quality. Cross-over studies did not present data in a way that could be included in the meta-analyses. 29 quality of life data (primary outcome measure) using validated measures, but only 15 reported useable data.	<ol style="list-style-type: none"> <li>1. A particular anticholinergic drug versus another in the management of OAB symptoms.</li> <li>2. Higher doses of anticholinergic drugs versus lower doses.</li> <li>3. Extended versus immediate release anticholinergic drugs.</li> <li>4. One route of anticholinergic drug administration versus another (e.g. oral, transdermal, rectal, intravesical).</li> </ol>

The reviewers concluded that there is little or no evidence available about quality of life, costs, or long-term outcome. A summary of the results can be seen in Table 3. According to this review, there were insufficient data from trials of other anticholinergic drugs (not covered in this table) to draw any conclusions.

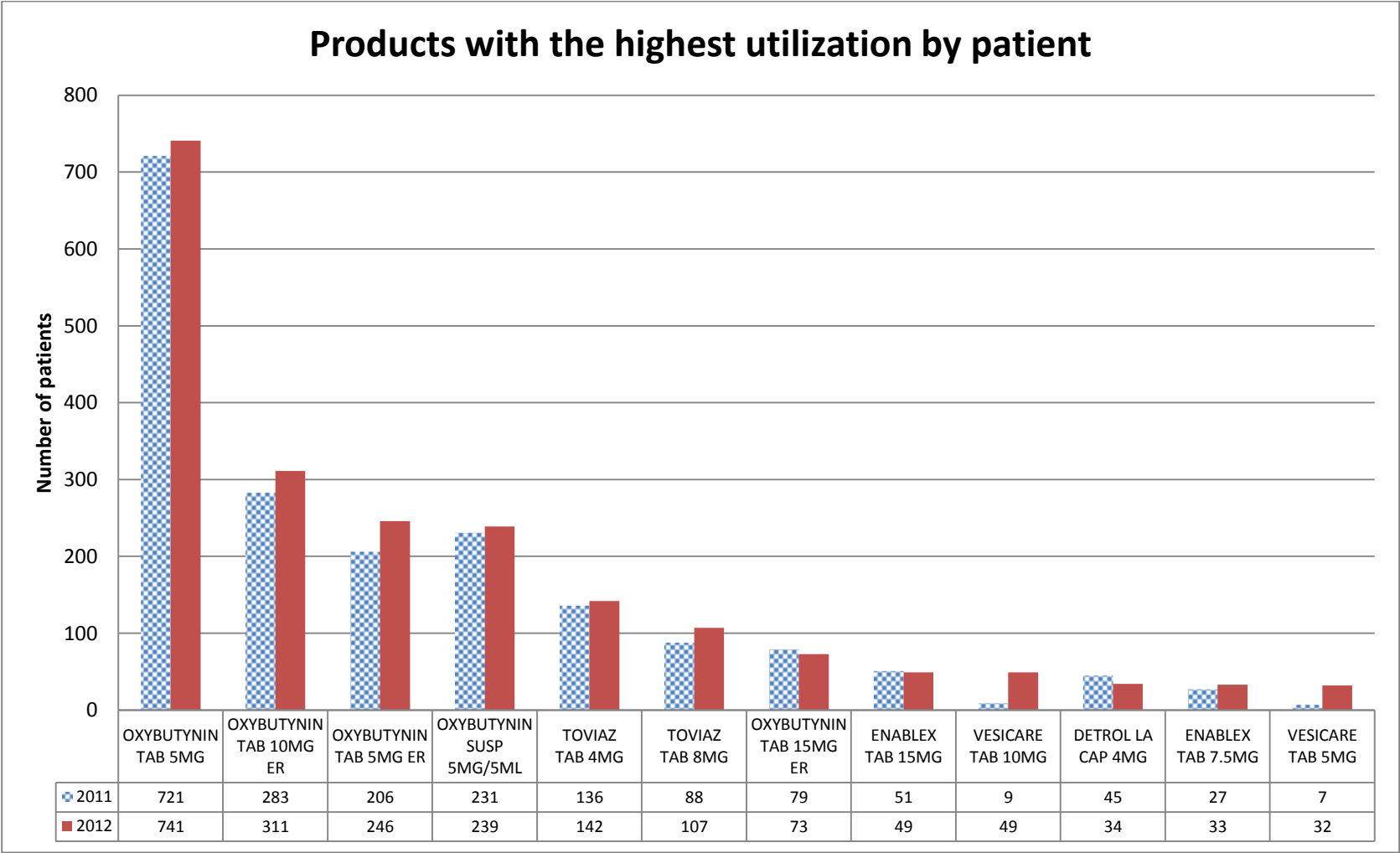
Table 3

COMPARISON	RESULTS				AUTHOR CONCLUSION
	Quality of life	Patient Reported Cure or improvement	Leakage episodes or voids in 24 hours	Adverse Effects	
<b>Oral IR: Tolterodine vs oxybutynin</b>	NS	NS	NS	Tolterodine: fewer withdrawals due to adverse events (RR=0.52; CI 0.40-0.66; 8 trials); Less dry mouth (RR=0.65; CI=0.60-0.71; 10 trials)	<b>Tolterodine</b> might be preferred for <u>reduced risk of dry mouth</u> .
<b>Solifenacin vs tolterodine</b>	Sign. favoring solifenacin (stand mean dif (SMD) - 0.12, 95% CI - 0.23 to -0.01; 3 trials)	Sign. favoring solifenacin (RR 1.25, 95% CI 1.13 to 1.39, 2 trials)	Sign. favoring solifenacin; leakage episodes in 24 hours (weighted mean dif (WMD) -0.30, 95% CI -0.53 to -0.08, 4 studies); urgency episodes in 24 hrs (WMD - 0.43, 95% CI -0.74 to -0.13, 4 trials),	No difference in withdrawals due to adverse events and dry mouth. After sensitivity analysis dry mouth (RR 0.69, 95% CI 0.51 to 0.94) was sign lower with solifenacin vs IR tolterodine	<b>Solifenacin</b> might be preferred for <u>better efficacy and less risk of dry mouth</u> (than IR tolterodine).
<b>Fesoterodine vs ER tolterodine</b>	Sign. favoring fesoterodine (SMD -0.20, 95% CI -0.27 to -0.14; 3 trials)	Sign. favoring fesoterodine (RR 1.11, 95% CI 1.06 to 1.16; 3 trials)	Sign. favoring fesoterodine: leakage episodes (WMD - 0.19, 95% CI -0.30 to -0.09), frequency (WMD -0.27, 95% CI -0.47 to -0.06) and urgency episodes (WMD - 0.44, 95% CI -0.72 to -0.16) in 24 hours	Fesoterodine: higher risk of withdrawal due to adverse events (RR 1.45, 95% CI 1.07 to 1.98); higher risk of dry mouth (RR 1.80, 95% CI 1.58 to 2.05) at 12 weeks.	<b>Fesoterodine</b> might be preferred for <u>superior efficacy</u> <b>but</b> has <u>higher risk of withdrawal</u> due to adverse events and higher risk of <u>dry mouth</u> .
<b>Comparisons of different doses of the same drug</b>					
<b>Tolterodine:</b> standard recommended starting dose (2 mg twice daily) vs two lower (0.5 mg and 1 mg twice daily), and one higher dose (4 mg twice daily).	N/a	N/a	Effects of 1 mg, 2 mg and 4 mg similar for leakage episodes and micturations in 24 hours	Greater risk of dry mouth with 2 and 4 mg doses at two to 12 weeks.	Usual starting dose: <b>2 mg</b> twice daily, but <b>1 mg twice daily</b> might be equally effective, with <u>less risk of dry mouth</u> .
<b>Solifenacin:</b> standard recommended starting dose (5 mg once daily) vs 10 mg			Frequency and urgency were less (better) with 10 mg compared to 5 mg,	Higher risk of dry mouth with 10 mg solifenacin at four to 12 weeks	Usual starting dose: <b>5 mg</b> once daily; this could be increased to <b>10 mg</b> once daily for <u>better efficacy</u> but with increased risk of <u>dry mouth</u> .
<b>Fesoterodine:</b> recommended starting dose (4mg once daily) vs 8 and 12 mg	N/a	Clinical efficacy (patient reported cure and leakage episodes & micturition per 24 hours) of <b>8 mg</b> was better than 4 mg. No sign dif in efficacy between 4 and 12 mg.		Higher risk of <u>dry mouth</u> with 8 mg (vs <b>4 mg</b> ); dry mouth sign higher with 12 mg at 8-12 weeks	N/a

Comparisons of immediate release (IR) versus extended release (ER) preparations					
ER vs IR oxybutynin or tolterodine or both	N/a	NS ( <i>few data</i> )	NS ( <i>few data</i> )	ER: less risk of dry mouth at 2-12 weeks	ER oxybutynin or tolterodine might be preferred to IR preparations because there is <u>less risk of dry mouth</u>
Comparisons of ER preparations (one ER vs another)					
Oral extended release: tolterodine vs oxybutynin	N/a	N/a	N/a	Less risk of dry mouth with <b>oral ER tolterodine</b> (RR 0.75, 95% CI 0.59 to 0.95)	N/a
Transdermal oxybutynin vs oral ER tolterodine	N/a	N/a	N/a	No difference between transdermal oxybutynin and oral ER tolterodine; some people withdrew due to skin reaction at transdermal patch site at 12 weeks.	N/a

Utah Medicaid Utilization Data

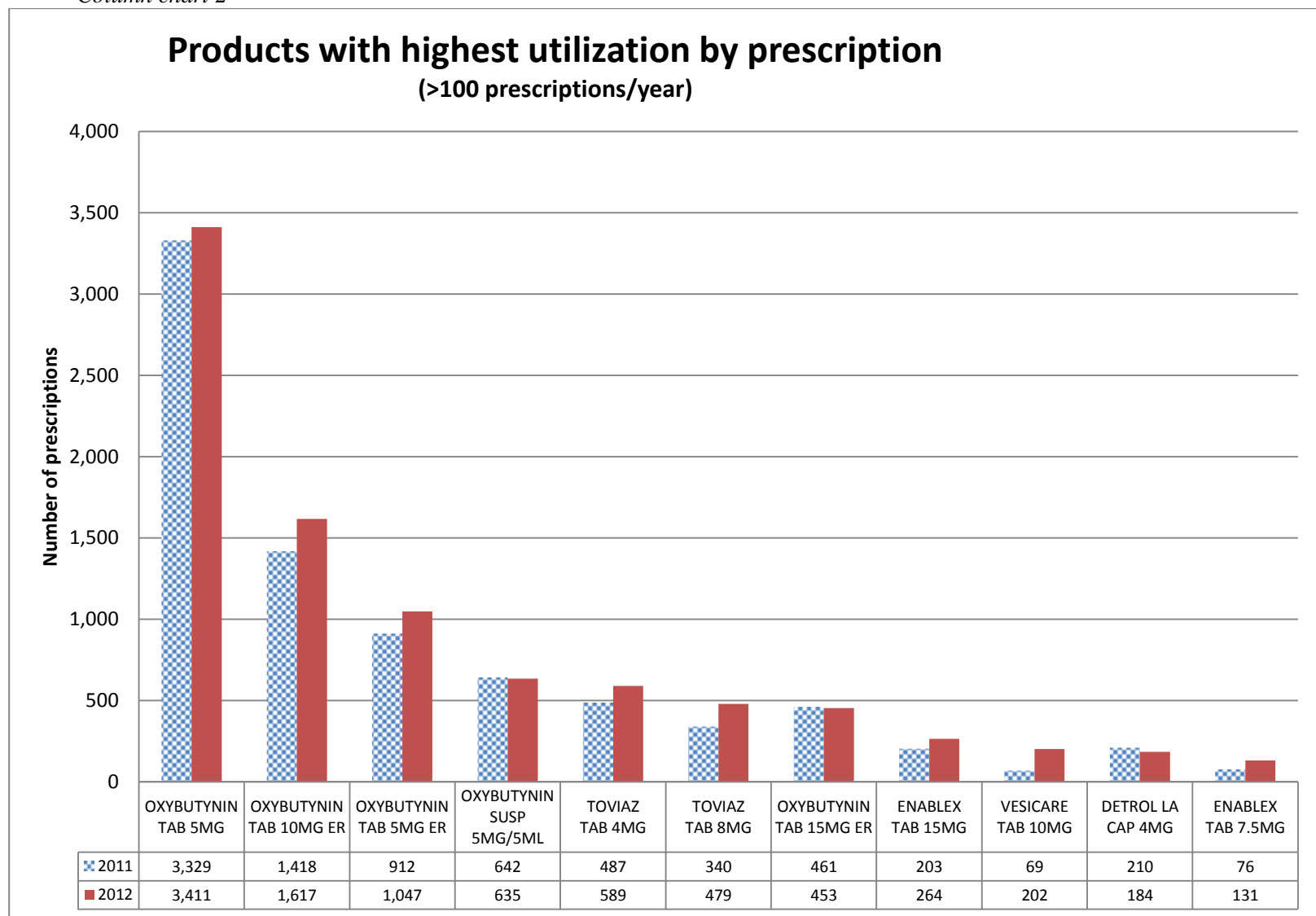
Column chart 1



Tolterodine 2 mg, trospium ER capsules, tolterodine 1 mg, Gelnique 3% gel and Ditropan XL had no utilization in 2011, but had some utilization in 2012 (very few patients and prescriptions).

Urispas (brand) and Ditropan IR (the brand name product for oxybutynin IR) were discontinued and there were therefore no prescriptions for this time period.

Column chart 2



## Conclusion

It is important to note that the AUA guideline states that OAB is not a disease, but a symptom complex that generally is not a life-threatening condition. After exclusion of other conditions that would require treatment, “no treatment’ is an acceptable choice made by some patients and caregivers.”<sup>2</sup> However, it is also a problem with psychological and social consequences and the benefits and risks/burdens of available treatment options to achieve symptom control needs to be considered.

Behavioral therapies should be first-line and may be combined with antimuscarinics. Antimuscarinics should be offered as second-line treatment. Currently, published literature does not support the use of one agent over another in terms of efficacy, but once daily dosing with extended-release agents tends to have fewer antimuscarinic side-effects than immediate release products.<sup>2,38-41</sup> Based on only a few studies, the guidelines state that transdermal oxybutynin patch or gel may be offered to patients who are at risk of or have experienced dry mouth with oral agents (low evidence strength; Grade C).<sup>2</sup>

Dose modification or a different anti-muscarinic may be tried when symptom control is inadequate and/or adverse effects are unacceptable and a few observational studies supports switching from older medication (oxybutynin<sup>43,45</sup> and tolterodine<sup>42,44,45</sup>) to newer medication (fesoterodine<sup>42</sup>, solifenacin<sup>43,44</sup>, and darifenacin<sup>45</sup>). Limited evidence exist that newer agents (e.g. Darifenacin) may cause less cognitive effects in the elderly.<sup>49,50</sup>

## Recommendations

Based on the information presented above, we make the following recommendation:

- All transdermal antimuscarinic (such as Gelnique and Oxytrol) prescriptions require a prior authorization

Prior authorization criteria could include the following:

Both 1 and 2 as well as at least one from 3-5.

1. Diagnosis code for overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency
2. Patient is within the age range for which the drug is FDA approved
3. Documentation of intolerance to a trial of at least 2 oral products (including an extended-release product)
4. Documentation of the inability of the gastrointestinal tract to absorb oral medications
5. Contraindication or intolerance / allergy to preferred oral products

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